Topic 10: Fundamentals of Drug Discovery and Development

Dr. Ron White
Senior Vice President
DMPK Science and Technology
Outline of the Seminar

• Unmet medical needs
• Where do new drugs come from?
• Nonclinical drug development
• Clinical drug development
• Registration with regulatory agencies
Overview of Drug Discovery and Development

- **Discovery** – starting with a therapeutic target (an unmet medical need such as colon cancer), select a biological target (e.g., the ras receptor), and design a molecule to bind to the target.

- **Development** – Test the experimental drug in human patients. A large effort is required to enable the clinical trials to test the drug candidate.

- **Registration** – Based on the results of clinical trials, apply to international regulatory agencies (e.g., US FDA) for approval to market the compound as a new drug for treatment of a defined disease condition.
Unmet Medical Needs

- **Cancer** (colon cancer, liver cancer, pancreatic cancer…)
- **Major Psychoses** (Schizophrenia, Bipolar Syndrome, …)
- **Neurodegenerative Diseases** (Alzheimer Disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Parkinson Disease,..)
- **Prion-based Diseases** (Bovine Spongiform Encephalopathy, “Mad Cow” Disease)
- **Drug-Resistant Microbial Diseases** (XDR-Tuberculosis, MRSA, …)
- **Tropical Diseases** (Malaria, Amoebic Dysentery, …)
- **Viral Infections** (HIV, HCV, H5N1 and H1N1 Flu, …)

We will discuss how to discover and develop new medicines to treat these diseases.
Where do new medicines come from?
Rational drug design

Medical Need (Therapeutic Target) → Molecular Target → In Vitro Model → ‘Hits’ → SAR → In Vivo Model → Lead Optimization → PK → Clinical Candidate

Biochemistry → Cell Biology → Bioinformatics → Genomics → Molecular Biology
Drug Discovery

Where do “Hits” come from?

- High throughput screening of chemical libraries
  - Natural products collections
  - Combinatorial chemistry
- Rational design
  - Based on structure of biological target
  - Based on structure of natural ligands
  - Based on structure of previous drugs
- Unexpected fortunate observations – discovery of ezetimibe (Zetia®)
Drug Discovery

“Hit-to-Lead” process

Structure-Activity Relationship (SAR)

Systematic variation of structure and measuring ligand affinity

Goal is to bring $IC_50$ down from 1-10 µM to 10-100 nM

Reduce number of chemical scaffolds

Original hits may have represented ten different chemical series

Identify two or three promising leads for further optimization
Drug Discovery

“Lead Optimization” process

Continue exploring SAR

Reduced number of chemical series

Goal is to bring IC\textsubscript{50} down to 0.1 - 10 nM

Counter screening (Selectivity)

Other high-throughput screens to make sure leads do not bind to undesirable targets (related receptors, ion channels, opioid receptors, kinases, etc.)

DMPK optimization (sometimes called ADMET)

DMPK has a separate SAR

Goal is to build in “drug-like” properties
Drug Discovery

“Drug-like” properties

**CHEMICAL**: Practical for large-scale synthesis; not too many stereo centers; not reactive

**BIOLOGICAL**: High affinity, selective ligand for a designated biological target, usually an enzyme or receptor

**PHARMACEUTICAL**: Soluble; stable; crystalline

**PHARMACOKINETIC**: Orally absorbable; distributes to the target organ; adequate persistence in the body; eliminated in a reasonable amount of time

**TOXICOLOGICAL**: Adequate margin of safety with respect to general toxicity and carcinogenicity

[Reference: White, Annual Reviews of Pharmacology and Toxicology 40: 133 (2000)]
<table>
<thead>
<tr>
<th>R1</th>
<th>Compound. Number</th>
<th>Human $K_i$ (nM)</th>
<th>% hERG inhibition @ 10 µM</th>
<th>Rat AUC @10 mg/kg (µM•hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>9.8</td>
<td>95</td>
<td>5.1</td>
</tr>
<tr>
<td>Me</td>
<td>2</td>
<td>0.3</td>
<td>44</td>
<td>4.4</td>
</tr>
<tr>
<td>iPr</td>
<td>3</td>
<td>1.6</td>
<td>37</td>
<td>0.5</td>
</tr>
<tr>
<td>cyclo-Pent</td>
<td>4</td>
<td>2.0</td>
<td>25</td>
<td>0.3</td>
</tr>
<tr>
<td>Ph</td>
<td>5</td>
<td>4.3</td>
<td>38</td>
<td>1.4</td>
</tr>
<tr>
<td>Cl</td>
<td>6</td>
<td>6.5</td>
<td>51</td>
<td>7.4</td>
</tr>
<tr>
<td>Br</td>
<td>7</td>
<td>1.5</td>
<td>5</td>
<td>6.2</td>
</tr>
<tr>
<td>Py</td>
<td>8</td>
<td>3.5</td>
<td>42</td>
<td>2.5</td>
</tr>
<tr>
<td>Im</td>
<td>9</td>
<td>1.1</td>
<td>49</td>
<td>7.2</td>
</tr>
<tr>
<td>SMe</td>
<td>10</td>
<td>0.9</td>
<td>4</td>
<td>0.2</td>
</tr>
</tbody>
</table>
End of Drug Discovery Process

After screening thousands of compounds, we select one compound to go into development.

A clinical candidate nomination document is prepared which contains pharmacological, chemical and DMPK assessment of the compound selected for development.

For example, the DMPK assessment of likelihood of clinical success:

- Preliminary plasma assay method (LC/MS/MS)
- Preliminary PK (IV and PO) studies in 3 species
- Metabolite profiles in animal and human hepatocytes
- Preliminary ADME in rats based on [³H]-drug candidate
- Preliminary plasma protein binding
- Preliminary CYP enzyme induction
- Preliminary CYP enzyme inhibition
- Estimation of clinical dose and PK
Development

Once a single compound has been identified by the Discovery process, the compound goes into Development.

• **Preclinical development**
  A number of activities must occur before an experimental compound can be given to human beings.

• **Clinical development**
  Clinical trials in which the safety and efficacy are determined in humans
Preclinical Development
Pharmaceuticals R&D

Select a salt form and crystalline polymorph based on physical characteristics such as solubility, long-term stability, hygroscopicity.

Devise a formulation

Solid-dosage form – must have good release characteristics and acceptable shelf-life.

If the dose is large and compound is poorly soluble, then solubilizing excipients must be added, making tablets or capsules very large.

For IV drugs, must find a vehicle with adequate solubility.
Preclinical Development
Chemical Process Research

• Scaling up the chemical synthesis from a few grams (lab scale) to a few kilograms (pilot plant) and eventually metric tons (manufacturing)

• The kilogram-scale process may be quite different from the lab-scale process used in discovery. The important criteria are cost-of-goods, minimal number of synthetic steps, consistency. This process must be established early so that batches used in preclinical tox studies and actual clinical trials have comparable impurity profiles.

• The manufacturing-scale process may have additional changes. “Green” processes are used as much as possible. Manufacturing is highly regulated by FDA to guarantee quality and consistent performance of the marketed medicine.
Preclinical Development

Drug Safety Evaluation

Animal toxicology studies are required before human dosing is allowed. Time and magnitude of exposure of the preclinical tox species to the compound must equal or exceed that of humans.

- Safety Pharmacology
- General toxicology
- Genotoxicity
- Reproductive toxicity
- Carcinogenicity
- Toxicokinetics (Bioanalytical)
Preclinical Development– Drug Safety

Safety Pharmacology

Perturbation of normal *in vivo* organ system function
Usually a single dose at several dose levels.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Animal Model</th>
<th>Endpoints Monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Dog, monkey or pig</td>
<td>HR, BP, ECG</td>
</tr>
<tr>
<td>CNS</td>
<td>Rat</td>
<td>Irwin Assay</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Rat</td>
<td>Rate and volume</td>
</tr>
<tr>
<td>G-I</td>
<td>Rat</td>
<td>Transit time, acid secretion, gastric emptying</td>
</tr>
<tr>
<td>Renal</td>
<td>Rat</td>
<td>Creatinine clearance, electrolyte excretion</td>
</tr>
</tbody>
</table>
Preclinical Development– Drug Safety

General Toxicology

Daily dosing at several dose levels for 1, 3, and 12 months in one rodent and one non-rodent species.

Goal is three-fold:
1. establish a dose that has toxicity (AEL)
2. establish a dose that has no toxicity (NOAEL)
3. determine the organ system that is most sensitive to the compound (target organ).

Endpoints:
Clinical signs during in-life phase
Clinical chemistry
Complete histopathology
Complete pathological exam of all organ systems
Preclinical Development– Drug Safety

Genotoxicity

Set of *in vitro* and *in vivo* tests of effect of compound on genetic systems.

For example:
- Ames test
- Mouse micronucleus
- Clastogenicity
Preclinical Development– Drug Safety

Reproductive toxicity

Effect of the compound on the reproductive systems of animals

Usually rats and rabbits

Determine:

- effect on fertility (ability to get pregnant)
- teratogenicity
- effect on ability to carry normal litter to full term
- ability of second generation to reproduce normally
Preclinical Development– Drug Safety

Carcinogenicity

Two-year study in both mice and rats. Dosed daily at two or three dose levels, including Maximum Tolerated Dose (MTD)

At end of in-life phase, complete pathological examination for presence of tumors
Preclinical Development

Bioanalytical

Must develop a fully validated, sensitive and specific assay for parent drug and any relevant circulating metabolites

Separate analytical method required for each species, biofluid and analyte

Almost always LC/MS/MS

Example:
Drug MW 500

This is the same technology used in the Olympics to detect illegal drug use.
Preclinical Development

Animal ADME (Absorption, Distribution, Metabolism, Excretion)

Goal is to demonstrate a thorough understanding of how the compound behaves in the body.

Definitive PK (IV and PO) studies in 3 species
\(^{[14]C}\text{-Compound ADME in Tox species}
Definitive plasma protein binding
Brain-to-plasma ratio
Food effect
Active or toxic circulating metabolites?
Definitive CYP reaction phenotyping
Definitive CYP induction
Definitive CYP inhibition
Effect of particle size, salt form, polymorphism on absorption
Rigorous prediction of clinical dose
Clinical Development

Comprises six distinct activities:

• IND Application (Regulatory approval to test in humans)
• Phase I Clinical Trials (Safety and PK)
• Phase II Clinical Trials (POC and dose selection)
• Phase III Clinical Trials (Large-scale efficacy)
• NDA Application (Regulatory approval to market)
• Phase IV (post-approval pharmacovigilance, etc.)
Clinical Development

Investigative New Drug Application (IND)

Request to test new experimental compound in humans

Summarize preclinical data package to justify request

Key points are to show:
- Plausible expectation that compound will benefit patients
- Evidence that the compound will not be toxic at therapeutic dose
- Demonstration of a means of controlled chemical synthesis of clinical-quality drug substance
Clinical Investigations

Objectives:
To assess whether a drug is of value in the treatment or prophylaxis of a disease or condition, its risks or undesirable effects, and the balance of risk and benefit.

Institutional Review Board (IRB):
Every clinical research institution must have an independent committee to review research to ensure that it is professional, ethical and lawful.

All clinical research studies require IRB approval.

Principles of Informed Consent:
A fair explanation of the procedure to be followed, and their purposes, including identification of any procedures which are experimental.

A description of any discomforts and risks reasonably to be expected.

A description of any benefits reasonably to be expected.
Phase I: Safety, Tolerability and Pharmacokinetics

Performed in normal healthy volunteers

What is “Safety”?  
What is “Tolerability”?  

Core studies
- Single ascending dose study (SAD)
- Multiple ascending dose study (MAD)
  - Drug-drug interaction studies
  - $[^{14}C]$-Radiolabel mass balance and disposition study
  - Age and gender effect study
  - Bioavailability study
  - Special populations (renal or hepatic impaired)
  - Other
- Each study reported to FDA
Safe Starting Dose for First-In-Human Study

FDA Guidance: First dose level in humans based on animal tox

<table>
<thead>
<tr>
<th>NOAEL (mg/kg/day)</th>
<th>HED (mg/m²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats 5</td>
<td>30</td>
</tr>
<tr>
<td>Dogs 3</td>
<td>60</td>
</tr>
</tbody>
</table>

Most sensitive species: Rats; apply Safety Factor of 10

Maximum safe starting dose: 3.0 mg/m²/day (0.081 mg/kg/day)

\[ 5.7 \text{ mg (70 kg subject)} \]

<table>
<thead>
<tr>
<th>Species</th>
<th>Body Mass (kg)</th>
<th>Body Surface Area (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>0.25</td>
<td>0.023</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
<td>0.51</td>
</tr>
<tr>
<td>Human</td>
<td>70</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Human Starting Dose = 5 mg
First-In-Human SAD PK

Single ascending doses of LXR-623, an experimental cholesterol-lowering drug given to normal, healthy volunteers

Phase II: Exploratory Efficacy and Safety Studies in Patients

- Controlled clinical trials designed to demonstrate effectiveness and relative safety.
- Normally performed on a limited number of closely monitored patients.
- This phase will seldom go beyond 100 - 200 patients
- Phase IIa: Proof-of-Concept (POC)
- Phase IIb: Dose selection for subsequent large-scale trials (Phase III), based on balance of safety and efficacy
- End-of-Phase II meeting with FDA (EOP2)
Phase III: Confirmatory Clinical Trials for Efficacy and Safety in Patient Populations

- Expanded controlled trials after basic efficacy has been established
- Depending on disease indication, number of enrolled patients ranges from a few hundred to ten thousand
- Intended to gather additional evidence of effectiveness for specific indications, and more precise definition of drug-related adverse effects
- Results seldom compared to placebo, but to “Standard of Care”
- Since diseases progress at different rates, a Phase III trial may require up to five years to show statistically significant efficacy
- In the past, some drugs have been approved based on surrogate markers, such as cholesterol lowering, rather than on clinical outcomes, such as reduced numbers of deaths from heart disease.
- Because of recent examples such as Vytorin®, FDA now requires actual clinical-outcome data for new approvals.
Registration

New Drug Application (NDA)

- Summary of the entire non-clinical and clinical data package
- Suggested disease indications (must have the data)
- Suggested patient groups to benefit (must have the data)
- Suggested dose, balancing safety and efficacy
- Proof that large-scale manufacture is controlled and consistently produces a high quality product
- Suggested product label (must have the data)
- Approval normally takes up to one year, but major advances in unmet medical needs may be accelerated
- Entire process from concept to NDA approval: 10-12 years
Post-Approval Development

Phase IV

- Larger and longer studies
  outcomes
  special populations
  comparator trials
- Expanded and new indications
  new patient groups and related diseases
- Pharmacovigilance
  monitor much larger patient population for safety signals
SUMMARY

• Many diseases still have inadequate treatments
• Modern medicines are designed, not “discovered”
• Many preclinical development activities must occur before a new drug candidate can be tested in humans
• Testing a new drug candidate in humans requires approval by an IRB and by a government regulatory agency such as U.S. FDA
• Clinical development has three experimental phases before approval
  – Phase I Safety and PK
  – Phase II Exploratory efficacy
  – Phase III Confirmatory efficacy
• If the drug candidate has a good balance of risk and benefit, it may be approved for marketing.